again binds as a dimer, but the consequence of the 'incorrect' spacing is that the two monomers in the dimer do not bind equivalently. Luisi *et al.* propose that one monomer binds specifically, whereas the other binds non-specifically.

The DBD, which is monomeric in solution[6,7], dimerizes when it binds to DNA, placing the recognition helices of each DBD in adjacent major grooves of the DNA. The two DBD domains make several protein–protein contacts where they meet between the two half-sites. These contacts appear to be the same in the two crystal structures. This region of protein is flexible in solution[6,7] and becomes structured only on binding to DNA, when it makes contacts with both the DNA and the other DBD. This accounts for the cooperative binding of two DBD domains to a GRE with the native three-base-pair spacing[8].

This new work confirms the arrangement of the protein–DNA complex that was predicted from NMR structures together with mutagenesis and biochemical studies[6,7]. In addition, this work reveals the precise chemistry of the protein–protein and the protein–DNA interfaces. Owing to the low resolution of the native GRE_{S3}–DBD complex, we must rely on the interactions seen on the 'specific' side of the high-resolution structure (DBD–GRE_{S4}). The protein is anchored to the phosphate backbone making a total of seven contacts on either side of the major groove. The DNA-recognition helix protrudes into the major groove, making three contacts to the base pairs. The DNA has a B-like structure, but at the 'specific' site the major groove is widened by about 2 Å to accommodate the recognition helix. The fitting of a DNA-recognition helix into the major groove of the DNA double helix is a recurring feature of sequence-specific recognition. (On the 'non-specific' side of the GRE_{S4} complex, the contacts made are rearranged and fewer in number.)

Many of the amino acids involved in DNA recognition, formation of the dimer interface, and maintenance of the three-dimensional structure have been identified by mutagenesis. In particular, three amino acids are responsible for discriminating between the glucocorticoid- and oestrogen-receptor half-sites (which differ by only two base pairs)[9–11]. These amino acids are glycine, serine and valine in the glucocorticoid receptor. Remarkably, only one of these residues makes contact with the DNA in the glucocorticoid receptor DNA complex. This is a van der Waals contact between a valine (alanine in the oestrogen receptor) and the methyl group of a thymine. Although the glycine is unlikely to make contact with the DNA, it seems surprising that the serine residue, which can make hydrogen bonds, is not involved.

An intriguing feature of the structure of the DBD–GRE_{S4} complex is that the protein–protein contacts at the dimer interface can override the potential specific protein–DNA contacts at the second site in the GRE, yet they are not strong enough to hold the protein as a dimer in solution[6,7]. There are two possible explanations for this. First, the protein–protein dimer interface might be induced and stabilized by interactions with the DNA backbone. Second, the high concentrations of protein and DNA in the crystallization conditions (that is, above the concentration of nonspecific binding) and crystal-packing forces might favour dimer formation.

The specific–nonspecific character of this complex arises because of the presence of an extra base pair between the two half-sites in the GRE. To obtain specific binding at both half-sites, the native spacing of three base pairs is required. Thus, as Luisi *et al.* note, the information contained in the spacing of the two half-sites is an integral part of the binding-site 'code', which is 'recognized' through the formation of a protein–dimer interface. This is especially important for other members of the nuclear-receptor family (the oestrogen, thyroid hormone, retinoic acid and vitamin D receptors), which recognize the same half-site sequence, but with different orientations and/or spacings[12,13]. For these receptors, orientation and spacing are the only means of discrimination.

So the new crystal structure gives us a detailed understanding of how the glucocorticoid receptor achieves specific binding to its target DNA binding site. But we must await the determination of similar structures for other members of the nuclear-receptor family, particularly those that bind to directly repeated half-sites, before we have the complete story. □

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DAEDALUS

The highway code

THE supermarket bar-code reader is diversifying into all sorts of routine tasks of sorting and identification. Daedalus now plans to import it into road transport. He is devising a downward-looking bar-code reader that scans the road under a vehicle, and a range of stencils for laying bar-code messages on the roads. The idea is to automate and extend the conventional system of road signs.

Road navigation would be transformed. Computerized routeing programs already exist, but are useless if you don't know at every instant where you are. Starry-eyed technomaniacs have suggested fitting every car with its own satellite navigator; but a simple bar-code road marking at each road junction would solve the problem far more directly. The vehicle's computer would not have to worry about absolute positions, and could find its way around the known road-network with absolute assurance. The most complicated and badly signposted cities, like London or Tokyo, would lose their navigational terrors. Bus and taxi drivers would no longer need elaborate training, and travelling salesmen could confine their mathematical efforts to routeing theory.

Even finer details could easily be encoded. Lane-identifiers could warn the driver to get into the correct lane for his destination, instead of having to veer across many lanes of enraged traffic for lack of local knowledge. Where appropriate, the bar-codes could even include the house numbers along the road. The familiar British ordeal of trying to drive safely, especially at night, while scanning the side of the road for distant, tiny, unpredictably placed, and quite possibly non-existent house numbers, would be mercifully ended.

Bar-coded roads would be safer, too. The local speed limit could be encoded, with the car's computer programmed to display increasingly disapproving messages if it was exceeded. Temporary bar-codes could be laid down to warn of diversions and lane closures. Even at night or in thick fog, an emergency bar-code mat laid on the road would reliably warn of an accident or emergency ahead. Bar-coded 'traffic lights', perhaps an LED or liquid-crystal display embedded in the road, could give far more information than three coloured lamps; if the driver failed to react to them, the vehicle's computer could set off a sequence of dire warnings. But the direst warning of them all could be set off by any bar-code at all — by being read backwards. This proof that the car was on the wrong side of the road should perhaps slam the brakes into an emergency crash-stop. DAVID JONES